# Cognitive recovery instead of decline after acute encephalitis: a prospective follow up study

Laura Hokkanen, Jyrki Launes

**Abstract**

***Objective*—Follow up of cognitive sequelae of acute encephalitis and estimation of the frequency of persisting dementia.**

***Methods*—Out of a series of 45 consecutive patients with acute encephalitis prospectively studied in 1990–95, 40 were screened for difficulty in everyday life using the Blessed dementia scale (BDS) 3.7 (1.4), mean (SD), years after onset. Eight patients had had herpes simplex encephalitis (HSVE), 16 some other identified aetiology, and in 21 the aetiology was unknown. All, except two patients with a non-herpetic encephalitis, were treated with acyclovir. All patients with disability in BDS (12/40), were invited to a neuropsychological reassessment, and the results of this assessment were compared with those of a similar assessment done after the acute stage. At follow up one patient could not complete the tests due to intractable epilepsy.**

***Results*—In six of 11 cases the symptoms causing disability were mainly psychiatric. Five patients (two with HSVE) had a pronounced memory impairment together with other cognitive deficits, indicating dementia (frequency of 12.8%). In eight of the 11 testable cases cognitive performance had improved over the years, in two cases a decline was found and one patient with severe deficits showed no change. Intractable epilepsy was found in four of 12 cases.**

***Conclusion*—Cognitive decline had taken place already at the acute stage, and further deterioration was uncommon. Considerable improvement occurred in most patients during follow up. Also in patients with HSVE treated with acyclovir the cognitive recovery was substantial and of a magnitude not expected based on previous literature. Intractable epilepsy contributed to the cognitive deterioration in some cases. Affective disorders also had a surprisingly important role for the long term outcome.**

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**Institute of Neuroscience, Department of Neurology, University of Helsinki, Finland**
L Hokkanen
J Launes

Correspondence to:
Dr Laura Hokkanen, Institute of Neuroscience, Department of Neurology, University of Helsinki, Finland.

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Encephalitides are known to cause severe cognitive decline in some patients. Among the acute encephalitides, Herpes simplex virus (HSV) has been the most commonly reported single aetiology leading to dementia.[1–3] Untreated herpes simplex virus encephalitis (HSVE) is fatal in up to 70%, and results in severe deficits in 40%–60% of the survivors.[4–7] Based on data published in the 1960s and 70s, the mortality in any encephalitis was 10%–50%, and 15%–28% of the survivors had neurological disability.[4 8 9] In the 1980s antiviral medication, improvements in neuroimaging, and probably also other developments in the neurointensive care seem to have improved the prognosis. Today the mortality in patients with HSVE treated with acyclovir is 19%–28%, but 18%–42% of survivors are still reported of having severe deficits in follow up.[10 11] Although the sequelae are mostly behavioural and cognitive, neuropsychological methods have not been systematically utilised. Cognitive deficits are often not detected in routine medical assessments. Even in cases with normal mini mental status examination, impairment has been found when a thorough neuropsychological assessment has been used.[12]

The damage caused by the herpes simplex virus to the CNS has been found to progress months after the acute stage in some cases untreated with antiviral medication.[13 14] Also, relapses after a seemingly favourable recovery after antiviral treatment have been reported.[15–17] Although this idea is not widely accepted,[18–20] the presumably progressive nature of HSVE has generated the idea of HSV having a role in Alzheimer's disease.[21 22]

To the best of our knowledge, no systematic follow up studies assessing the cognitive performance of a group of patients after acute encephalitides exist in the English literature. Previously we found that cognitive impairment initially occurs in 88% of the HSVE and in 56% of the non-HSV encephalitic patients.[23] We now aimed to study (1) does progressive deterioration really occur after acute encephalitis, or (2) do the cognitive deficits found in the acute stage later improve, and (3) how often acute encephalitides cause dementia?

## Materials and methods

PATIENTS

Forty five consecutive patients with acute encephalitis were prospectively studied between 1 January 1990 and 31 December 1994. The mean (SD) age of the patients was 40.8 (16.3) years (range 19 to 73), and the average length of the education was 11.0 (3.9) years. Twenty six of the patients were men, 19 women.

The diagnosis of encephalitis was based on clinical picture with symptoms and signs

suggesting the involvement of brain parenchyma, EEG findings compatible with encephalitis, CSF findings compatible with infection of the CNS and CT excluding other intracranial causes. Standard laboratory tests were performed to exclude system disorders and generalised infections. Patients with alcohol misuse, and with coexisting or previous neurological disease were excluded. The microbial aetiology was verified in 24 (53%) patients. The diagnosis was established as described earlier.[23] Eight patients had HSVE, seven had herpes zoster encephalitis, nine had some other specified aetiology, and in 21 cases the causative agent was unidentified.

Forty three patients, including all patients with HSVE, were given intravenous acyclovir (30 mg/kg per day) for 11.0 (3.0) days. Acyclovir was started in 3.5 (4.5) days after the onset of first brain symptoms in all patients. In the patients with HSVE acyclovir was started within 24 hours in five, within two days in two, and within four days in one case. One patient was diagnosed as having epidemic nephropathy and one was strongly suspected of having tuberculous meningoencephalitis. These patients were treated accordingly and received no acyclovir. Ten patients had antiepileptic medication at discharge.

During follow up, EEG and standard laboratory tests were performed on all patients. Follow up CT or MRI was performed on 29 patients. Hospital records of neurological or psychiatric treatments during the follow up were also obtained.

### ASSESSMENT OF DEMENTIA AND DISABILITY IN DAILY LIFE

To screen for patients with persisting disability, a questionnaire was sent to all patients in October 1995 (44.7 (16.3) months, after the onset of symptoms). The patients were asked about their current emotional, cognitive, and somatic complaints, as well as their employment status. A family member was asked to rate changes in the patient's performance in everyday activities, and habits by employing the Blessed dementia scale (BDS).[24] As well as the cognitive changes and activities of daily living, the BDS assesses personality and emotional changes, apathy, and withdrawal. This rating was used as the outcome measure in the follow up. In BDS higher points indicate a higher degree of disability. Four points or more of the maximum total of 28 was considered to indicate pronounced disability (unfavourable outcome), a rating of less than four points to indicate normal performance and favourable outcome.[25] The questionnaire was returned in 40 of 45 cases (89%). According to the medical files, all five who did not reply had returned to gainful employment within a year after onset.

Dementia was diagnosed according to the DSM-III-R criteria.[26] Pronounced memory impairment in combination with loss of other cognitive functions significantly interfering with social and occupational functioning was required. Memory impairment was considered substantial when the Wechsler memory quotient (MQ) was below 95, the lower limit of the normal average in the Finnish norms.[27]

*Table 1 The neuropsychological test battery used in follow up, these 18 subtests were also used for calculating the test performance index*

| |
|---|
| Intellectual functions: |
| 1 WAIS information*[55] |
| 2 WAIS arithmetic* |
| 3 WAIS vocabulary* |
| 4 WAIS digit symbols† |
| 5 WAIS picture completion† |
| 6 WAIS block design† |
| Memory: |
| 7 WMS logical memory[56] |
| 8 WMS associative learning |
| 9 WMS visual reproduction |
| 10 The Benton visual retention test[57] |
| Language abilities: |
| 11 Comprehension of sentences with complex semantic structures[58] |
| 12 Confrontation naming of pictures and body parts |
| Visuopractic abilities: |
| 13 Copy of a cube and a Greek cross |
| 14 Clock hand task |
| Attention and executive functions |
| 15 WMS mental control |
| 16 The Stroop colour naming time[59] |
| 17 The Stroop clour-word interference time |
| 18 Word fluency: oral output of words beginning with a letter K in one minute (modification of FAS[60]) |

* For the estimation of the verbal IQ.
† For the estimation of the performance IQ.
WAIS = The Wechsler adult intelligence scale; WMS = The Wechsler memory scale.

### EVALUATION OF THE COGNITIVE DEFICITS

#### *Neuropsychological appraisal*

A thorough neuropsychological evaluation was first carried out at a mean of 26.5 (20.8) days (range 5–115) after the onset of symptoms, as soon as the patient could cooperate adequately. All patients with reported disability (the unfavourable outcome group) were invited to a neuropsychological re-examination, which was carried out using the same protocol as in the first investigation.

Table 1 shows the 18 neuropsychological subtests. The test battery was constructed following the guidelines for the assessment of dementia.[28] One patient was assessed using a Luria based dementia battery (D-test) to avoid a floor effect due to a marked cognitive decline. The D-test includes subtests of orientation, memory and intellectual functions, as well as tasks of naming, semantic comprehension, and visuopractice and motor functions.[29 30] Depression was assessed with the Beck depression inventory[31]; scores above 17 were considered to suggest depression.[32] The significance of the change in the patients' performance during follow up was analysed using the non-parametric Wilcoxon matched pairs test. Also, we calculated a Test performance index (TPI) separately for both assessments. This was done by counting the number of subtests where the patient's performance was within the normal range (maximum value 18 indicating intact performance).

#### *Normative data*

The normative data for the neuropsychological tests was obtained from a group of healthy controls (n=25) who were tested once. The control group, who initially had volunteered for a study of quantitative EEG at the Institute of

*Table 2 Persisting symptoms in 12 patients with reported disability in the follow up*

| Case No | Sex | Age at onset | Aetiology | Neurological symptoms | Emotional symptoms | Memory deficit (MQ < 95) | Status at follow up |
|---|---|---|---|---|---|---|---|
| 1 | M | 26 | HSVE | − | + | − | Employed |
| 2 | M | 47 | HSVE | − | + | − | Employed |
| 3 | F | 56 | HSVE | − | + | + | Retired |
| 4 | M | 60 | HSVE | Epilepsy | − | + | Retired |
| 5 | M | 19 | Adenovirus | − | + | − | Employed |
| 6 | M | 23 | Unknown | Epilepsy | − | NT | Retired |
| 7 | M | 35 | Unknown | Epilepsy | + | + | Retired |
| 8 | M | 49 | Unknown | Right sided weakness | + | − | Retired |
| 9 | F | 55 | Unknown | − | + | − | Retired |
| 10 | F | 66 | Unknown | Epilepsy | − | + | Retired earlier |
| 11 | M | 66 | EN | − | + | − | Retired earlier |
| 12 | M | 70 | HZE | − | − | + | Retired earlier |

HSVE = Herpes simplex encephalitis; EN = epidemic nephropathy caused by the Puumala virus; HZE = herpes zoster encephalitis; NT = not testable; + = deficit; − = normal.

*Table 3 The employment status at follow up of all 45 patients*

| Aetiology | Status at onset | Employment status | Favourable outcome | Unfavourable outcome | Non-responders | Total |
|---|---|---|---|---|---|---|
| HSVE | Working | Working | 1 | 2 | 2 | 5 |
| | Working | Not working | 0 | 2 | | 2 |
| | Not working | Working | 0 | 0 | | 0 |
| | Not working | Not working | 1 | 0 | | 1 |
| Others | Working | Working | 16 | 1 | 3 | 20 |
| | Working | Not working | 2 | 4 | | 6 |
| | Not working | Working | 2* | 0 | | 2 |
| | Not working | Not working | 6 | 3 | | 9 |
| All | Working | Working | 17 | 3 | 5 | 25 |
| | Working | Not working | 2 | 6 | | 8 |
| | Not working | Working | 2* | 0 | | 2 |
| | Not working | Not working | 7 | 3 | | 10 |
| Total | | | 28 | 12 | 5 | 45 |

* Two patients who initially had been housewives, had started working full time.

Occupational Health, were 42.9 (13.5) years of age, and had on average 12.2 (2.7) years of education. The age and education of the controls were not significantly different from those of patients (Student's *t* test). The cut off point for impairment in each subtest was determined to be the score 2 SD below the mean of the control group. In tests, in which the controls scored close to maximum points (SD<1.0) the lowest value of the controls was used as the cut off point.

## Results

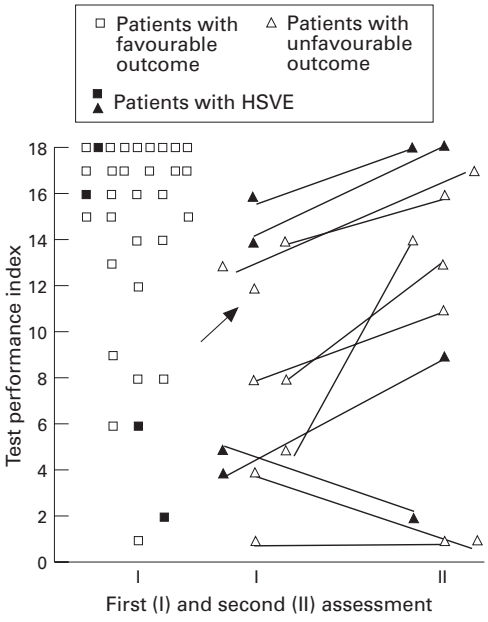
### THE OUTCOME GROUPS

The mean score of the BDS in the 40 responders was 3.9 (5.1), range 0–20. Twenty eight (including two HSVE) patients had a BDS score below 4, indicating normal performance in everyday activities (favourable outcome group). Twelve (30%) had a BDS score above 4, indicating disability (unfavourable outcome group, table 2). The unfavourable outcome group was older at the time of the onset than the favourable outcome group (47.7 (17.9) *v* 37.3 (16.3) years, respectively), although the difference was not significant (Student's *t* test). Table 3 shows the employment status of all 45 patients. Two of the 28 patients in the favourable outcome group had not been able to return to their previous occupation, one because of intractable epilepsy and one because of depression. The frequency of return to work was 90% in the favourable outcome group (seven had retired before the onset). In the unfavourable outcome group the frequency was 33%, which was significantly less (Fisher's exact test P<0.01). There were four patients with intractable epilepsy in the unfavourable outcome group (33%) and only one in the favourable outcome group (3%) (Fisher's exact test P<0.05). However, there was no difference in the number of patients having permanent antiepileptic medication in these groups (Fisher's exact test).

### NEUROPSYCHOLOGICAL APPRAISAL

The figure shows the TPI (the number of tests with normal performance) for the first and for the follow up assessment. In the selected group the neuropsychological re-evaluation was carried out at a mean of 36.6 (13.2) months after the onset (range 19–60). Patient 6 could not complete the test battery because of frequent epileptic seizures. An increase in the TPI was found in eight out of 11 re-examined cases. In one case (patient 10) there was no change and in two (patients 4 and 12) there was decrease in performance. The follow up assessment discovered pronounced memory impairment together with other cognitive deficits in five of the 11 patients (table 2).

Table 4 shows the group means of the 18 neuropsychological subtests initially and in the follow up. Case 6, who could not complete the tests, and case 12, who was assessed using a different test battery, are not included in this table. An increase in the mean performance was seen in 15 of the 18 subtests, and the improvement was statistically significant in WAIS digit symbols ($z$=1.95, P<0.05), Wechsler memory scale associative learning




*The test performance index (TPI) is expressed as the number of tests, out of a total of 18, in which the patient performed within the normal range. The first column shows the TPI scatter of patients with favourable outcome, who were not re-examined. The second column shows the TPI scatter of the first assessment of patients with unfavourable outcomes. The third column shows the TPI scatter of the second assessment of these patients. Black symbols indicate patients with HSVE. One patient (arrow) was untestable in follow up because of frequent seizures.*

*Table 4 The results of the first and follow up assessments in 10 of 12 patients with unfavourable outcome after encephalitis (one excluded patient was tested with a different test battery and another was untestable due to frequent epileptic seizures)*

| *Variable* | *First mean (SD)* | *Second mean (SD)* | *P value* | *Control mean (SD)* |
|---|---|---|---|---|
| Information* | 10.6 (3.5) | 11.2 (3.9) | | 13.6 (2.6) |
| Arithmetics* | 10.0 (3.6) | 10.3 (3.7) | | 12.5 (1.5) |
| Vocabulary* | 10.5 (4.8) | 12.0 (4.4) | | 13.7 (2.2) |
| Digit symbols* | 5.9 (3.8) | 7.9 (4.7) | P<0.05 | 13.1 (3.0) |
| Picture completion* | 10.0 (3.1) | 10.6 (3.7) | | 12.2 (2.0) |
| Block design* | 7.2 (4.3) | 8.4 (5.7) | | 12.1 (2.8) |
| Logical memory† | 6.4 (4.8) | 7.8 (4.8) | | 12.7 (2.9) |
| Visual reproduction† | 4.9 (3.3) | 7.5 (5.0) | | 11.7 (2.5) |
| Associative learning† | 9.0 (4.2) | 13.9 (5.6) | P<0.01 | 18.7 (2.5) |
| Benton VRT‡ | 5.0 (2.6) | 4.9 (2.6) | | 8.0 (1.1) |
| Sentence comprehension | 9.8 (1.5) | 9.6 (2.1) | | 10.8 (0.5) |
| Naming | 30.3 (7.3) | 33.0 (3.2) | | 34.9 (0.2) |
| Copying | 33.0 (6.3) | 34.8 (8.2) | | 38.9 (0.2) |
| Clock hands | 21.7 (2.9) | 22.0 (3.0) | | 23.8 (0.4) |
| Mental control† | 4.5 (2.9) | 5.0 (2.5) | | 6.4 (2.1) |
| Colour naming§ | 88.6 (22.8) | 89.9 (56.1) | | 52.9 (7.2) |
| Colour word naming§ | 226.5 (152.8) | 217.0 (197.4) | | 94.4 (19.2) |
| Word fluency | 11.5 (4.5) | 17.1 (8.4) | P<0.05 | 22.2 (4.9) |

The significance of the difference in the patient means was tested with Wilcoxon matched pairs test. The means of the control group are given for comparison.
* The WAIS, scaled score.
† The WMS.
‡ The Benton visual retention test, correct pictures.
§ The Stroop test, time in seconds.

($z$=2.67, P<0.01), and verbal fluency ($z$=1.99, P<0.05). There was no statistically significant decrease in the mean performance in any of the subtests.

PSYCHIATRIC SEQUELAE

Eight patients had suffered from emotional instability or personality change during follow up (table 2). The psychiatric symptoms included panic disorder and anxiety in patient 1, bipolar affective disorder with predominantly manic behaviour in patient 2, aggressive outbursts and irritability in patients 3 and 5, and depression in patients 7, 8, 9, and 11. Klüver-Bucy syndrome was not encountered.

## Discussion

Psychometric testing alone is not adequate for diagnosis of dementia when the DSM-III-R criteria[26] are used. Social competence and behaviour must also be assessed—for example, by using behavioural rating scales or questionnaires. The BDS rated by a family member has been validated for dementia screening. In the validation study the cut off point of 4 gave a sensitivity of 90% and specificity of 84% for dementia.[25] The Blessed scale has been found to correlate with neuropathological changes[24] and it has been used for measuring longitudinal changes in the functional capacity in dementia.[33] However, it is less reliable in predicting the cognitive test performance because psychiatric symptoms are also included in the total score.

The accuracy of data gained by mailed questionnaires may be limited by a high drop out rate. In this study 89% returned the query, which is adequate for a reliable analysis. Furthermore, as the non-responders had previously reported to have returned to their previous employment, we think that we have found all demented patients in this series.

The 28 patients with favourable outcome included patients who initially had substantial cognitive deterioration (low TPI). Although they were not re-examined, it is likely that some neuropsychological deficits still persist in these patients. However, they were reported to be independent in everyday activities by their family members, and therefore they do not fill the DSM-III-R criteria for dementia. Young age may be a positive prognostic factor in encephalitis.[34] The patients with favourable outcome were on average younger than the patients with unfavourable outcome.

Twelve out of 40 responders had difficulty in daily activities. At re-examination, five of them had persisting memory defect and other cognitive deficits. One patient in the unfavourable outcome group could not be re-tested due to frequent seizures. Thus the frequency of dementia was 12.8% among the re-tested responders, and 11% among the total sample of 45. The follow up time (about 3.7 years) is still relatively short, and possibly in the long run some of the patients will develop dementia. It has been suggested that patients with brain injury (or other lesions) may be more susceptible to the effects of aging. An association between remote brain injury (latencies up to 30 years) and Alzheimer's disease has recently been found in a longitudinal incidence study.[35] In single cases, however, it is extremely difficult to establish the causal relation between an earlier neurological disease and dementia appearing decades later.

The frequency of dementia after encephalitis does not seem to be higher than after stroke or brain trauma according to the literature. However, comparisons are difficult due to differences in the definitions of dementia and study protocols. In one cross sectional study with stroke patients the frequency of dementia was as high as 58% in patients having only one ischaemic event.[36] On the other hand, in a four year longitudinal study the frequency of dementia after a single stroke was only 6%.[37] In brain injury, the frequency of dementia according to one follow up study was 21%.[38] Our figure of 12.8% falls within these boundaries. Also the trend in recovery is comparable with other patient groups. The performance in a single memory test followed up for 5–10 years after brain trauma showed no change in 58%, improved in 31%, and deteriorated in 11% of the patients.[39] In our study the cognitive symptoms after encephalitis improved in eight of 11 (73%) patients. Two of the 11 patients (18%) deteriorated over the years, and one initially severely affected patient (9%) did not change.

Unfavourable outcome was not caused by cognitive decline only. Six of the 12 patients with unfavourable outcome had changes in personality and mood, which were severe enough to interfere with daily living. Three of the six performed within the normal range in almost all neuropsychological measures at re-examination, and were also employed in their previous occupation. Minor neuropsychological impairment was found in the three other cases, but mainly the problems were caused by the persisting mood change. These psychiatric symptoms can on the one hand be explained by an emotional reaction to a

possibly fatal illness, whereas on the other hand symptoms may also be due to damage to the limbic system caused by encephalitis. In particular HSVE is known to affect the limbic structures,[40–42] resulting sometimes in severe changes in behaviour and personality, including the Klüver-Bucy syndrome.[43–45] Affective disorders may also occur after herpes zoster[46 47] and other viral encephalitides.[48–50]

Four patients in the unfavourable outcome group had intractable epilepsy. It may be argued that the frequent seizures contributed the most to the cognitive decline in these cases. It has been shown that high seizure frequency may have a detrimental effect on cognitive functioning.[51–53] Memory performance especially may deteriorate because of epilepsy related neuron loss in the hippocampus.[54] Epilepsy does not invariably lead to poor outcome, however. In our material one patient was rated independent in everyday activities despite frequent seizures. This young patient, as well as his family, agreed that apart from the ictal and postictal confusion, he performed normally.

In our series the cognitive outcome of patients with HSVE was more favourable than would be expected based on the literature.[12 42] This may be due to starting acyclovir therapy within four days of the onset, which was made possible by the general awareness of encephalitis and the improvements in neuroradiological methods (MRI and CT). Two out of eight of our patients with HSVE were close to normal in the first neuropsychological assessment, and two recovered in follow up to be rated to perform normally in everyday situations. Four were re-examined because of reported difficulty in everyday life but only two were found to have persisting cognitive deficits. One of them had deteriorated during follow up. Altogether five (71%) of the seven patients with HSVE who initially were not retired, were eventually able to retain gainful employment. It has been argued that acyclovir treatment decreases the mortality but increases the relative frequency of cognitive deficits in surviving patients.[44] Our findings suggest that this is not true.

In conclusion, after an average follow up of 3.7 years, the frequency of dementia was 12.8% in 40 consecutive patients with acute encephalitis. In most patients the cognitive decline had taken place already at the acute stage. The cognitive performance improved in all but three cases, two of whom had frequent seizures. Seventy seven per cent of employed patients had returned to their previous occupations.

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